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1. Khuri et al. Journal of Thoracic and Cardivascular Surgery. 1988, 95:442-454.

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The superiority of continuous cold blood cardioplegia in the metabolic protection of the hypertrophied human heart

The effects of sanguineous and asanguineous cardioplegia on the generation of myocardial acid in the hypertrophied human heart during aortic clamping and reflow were elucidated by continuous intraoperative monitoring of myocardial pH in 42 patients undergoing valve replacement, with or without coronary bypass. The patients were divided into three groups: Group I (n = 14) received intermittent crystalloid cardioplegia; group II (n = 14) received intermittent blood cardioplegia; and group III (n = 14) received continuous blood cardioplegia. The groups were matched according to six previously elucidated determinants of myocardial acidosis. Measurements were made of myocardial pH, hydrogen ion concentration ([H+]), and the difference in pH units between myocardial pH and the pH of neutrality of water at the corresponding temperature (ΔpHn). Throughout aortic clamping, myocardial pH in groups I and II fell significantly by 0.46 ± 0.08 and 0.15 ± 0.07 units, respectively ($p < 0.001$ between the groups). In contrast, myocardial pH remained statistically unchanged throughout aortic clamping in group III ($p < 0.001$ compared to groups I and II). Similar relationships were observed in [H^+] and ΔpHn during aortic clamping. During the early reflow, myocardial acidosis was observed in all three groups and ΔpHn in group III increased from −0.26 ± 0.10 at the end of aortic clamping to −0.57 ± 0.07 during reperfusion ($p < 0.03$). Patients in groups II and III required significantly less inotropic and mechanical cardiac support than patients in group I ($p = 0.017$). Hence, although continuous blood cardioplegia does not completely prevent acid accumulation during reflow, it provides better metabolic protection of the hypertrophied human heart than either intermittent crystalloid or intermittent blood cardioplegia.

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The relative efficacy of sanguineous versus asanguineous cardioplegic solutions in achieving optimal protection of the myocardium during cardiac operations has been debated in numerous publications. Most of the published animal studies have demonstrated a superiority of sanguineous over asanguineous solutions in preserving myocardial high-energy phosphates,[1-7] myocardial function,[1,4-9] and myocardial ultrastructure.[4,10] Clinical studies comparing sanguineous and asanguineous cardioplegic solutions have been relatively less conclusive; some have demonstrated a clear advantage of sanguineous solutions[11-14] whereas others have shown no differences in the myocardial protective efficacy of the two solutions.[15-19] The sanguineous versus asanguineous cardioplegia controversy remains unsettled; the comparative clinical studies that addressed it were all performed on relatively low-risk patients undergoing coronary revascularization. These studies used limited methods, none of which provided an on-line intraoperative metabolic assessment of the adequacy of myocardial protec-

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Table I. *Characteristics of the patients studied*

	Group 1	*Group 2*	*Group 3*	*p (AOV)*
No. of patients	14	14	14	
Age (yr)	65 ± 1.23	58 ± 2.07	61 ± 2.69	NS
LV mass (gm)*				
Range	220-674	174-627	272-594	
Mean	453 ± 35	344 ± 43	409 ± 57	NS
Preop. LVEDP (mm Hg)	21.4 ± 2.8	21.2 ± 2.1	26.3 ± 2.4	NS
Preop. EF (%)	49.5 ± 3.1	48.2 ± 3.7	47.4 ± 3.7	NS
Procedures				
AVR	3	5	7	
MVR	3	2	1	
AVR + CABG	6	2	5	
MVR + CABG	0	2		
AVR + MVR	2	2	1	
AVR + MVR + CABG	0	1		
	14	14	14	

Legend: AOV, Analysis of variance; NS, Not significant; AVR, aortic valve replacement; MVR, mitral valve replacement; CABG, coronary artery bypass graft; LV, left ventricular; LVEDP, left ventricular end-diastolic pressure; EF, left ventricular ejection fraction.

*Normal left ventricular mass is 160 gm.

We[20-22] have previously shown that the intraoperative on-line measurement of intramyocardial pH provided a reliable assessment of the adequacy of myocardial preservation during cardiac operations in man. Using this methodology and combining it with the ultrastructural analysis of left ventricular biopsy tissue obtained in the course of valvular operations,[23] we demonstrated the failure of a standard crystalloid cardioplegia regimen to secure optimal protection of the *hypertrophied* left ventricle. In a concomitant experimental study in the dog model, we demonstrated the superiority of a sanguineous cardioplegic solution over an asanguineous solution in the prevention of myocardial tissue acidosis during the period of aortic clamping.[24] Hence this study addresses the sanguineous/asanguineous cardioplegia controversy by examining, in a group of relatively high-risk patients with left ventricular hypertrophy, the relative efficacy of three modalities of myocardial protection (intermittent crystalloid cardioplegia, intermittent blood cardioplegia, and continuous blood cardioplegia) in the prevention of myocardial acidosis during and after the period of aortic clamping in the course of valvular heart operations.

Patients and methods

To date, continuous intraoperative measurements of intramyocardial pH were obtained in 178 patients undergoing cardiac operations at our institution. All the operations were performed by two surgeons employing the same surgical team and identical techniques. In the first 115 patients, intermittent cold crystalloid potassium cardioplegia was routinely used for myocardial protection. Subsequently, intermittent and continuous [illegible] cardioplegia

patients with left ventricular hypertrophy undergoing valve replacement. This study comprises three matched groups of 14 patients each, representing the three types of myocardial protective techniques used. All 42 patients in the study had evidence of left ventricular hypertrophy and underwent valve replacement with or without coronary revascularization between July 3, 1984, and March 1, 1987 (Table I).

Operative technique. Through a median sternotomy, cardiopulmonary bypass was instituted by cannulating the ascending aorta with an 8 mm cannula (Sarns Inc., Ann Arbor, Mich.) and the right atrium and inferior vena cava with a Sarns two-stage cannula. For patients undergoing mitral valve replacement, the venae cavae were cannulated separately with No. 34 and 36 Sarns venous cannulas. The patients were cooled to 25° C. The left ventricle was vented in all patients either through the right superior pulmonary vein or through the left ventricular apex. The aorta and the pulmonary artery were cross-clamped with a single Fogarty clamp. The cardioplegic solution was then administered as described below: An insulator pad (Shiley Incorporated, Irvine, Calif.) was placed behind the heart and topical cooling with iced slush was applied. In patients requiring coronary artery bypass grafting, revascularization was performed before valve replacement. The distal anastomoses were performed with segments of saphenous vein; their free ends were then connected to tubing through which cardioplegic solution was infused (Fig. 1). After valve replacement (and closure of the aorta or left atrium, or both), the aortic clamp was released and rewarming was started. The proximal anastomoses were then performed and the heart was defibrillated during the period of rewarming. Temporary ventricular pacing was instituted if heart block was encountered. Weaning from cardiopulmonary bypass was usually performed at a systemic temperature of 38° to 39° C. For inotropic support during the weaning process, dopamine was used as the initial drug, followed if need be by epinephrine (in combination with nitroprusside in most cases). Significant inotropic support was defined as [illegible]

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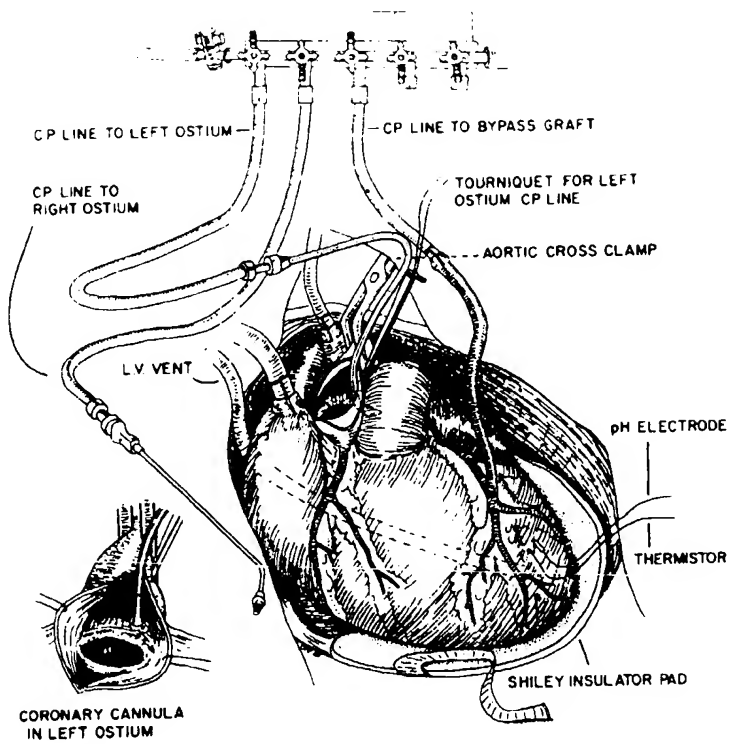

Fig. 1. Cardioplegia *(CP)* was simultaneously delivered to the left and right coronary ostia and, after completion of the distal anastomoses, to the free ends of the saphenous vein grafts. The initial dose of cardioplegic solution was administered into the aortic root through a separate cannula. The left ventricle *(LV)* was vented through either the right superior pulmonary vein or the apex. An insulator pad was placed along the posterior wall of the ventricle. Myocardial pH and temperature were measured in the anterior wall of the left ventricle.

need for epinephrine in any dose. When these pharmacologic agents failed, intra-aortic balloon counterpulsation was instituted.

Techniques for administering cardioplegic solution. In patients requiring mitral valve replacement, cardioplegic solution was delivered through the aortic root via a 12-gauge cardioplegia catheter (Sarns). In patients undergoing aortic or double valve replacement without coronary revascularization, a silicone rubber Spencer-Malette cannula (Dow Corning Corp., Midland, Mich.), connected to cardioplegia tubing, was placed in the orifice of the left main coronary artery and fixed to the aortic wall with a 4-0 Prolene suture and a fine tourniquet (Fig. 1). In addition, a single bolus of 500 to 800 ml of cardioplegic solution was given through the orifice of the right coronary artery via a hand-held cannula. In patients undergoing aortic or double valve replacement with revascularization, the cardioplegic solution was initially administered through the ascending aorta. When the aortic root was opened, cardioplegic solution was administered into the coronary ostia as just described. The patients were divided into three groups depending on the type and mode of administration of the cardioplegic solution used.

Group I (14 patients operated on between July 3, 1984, and [illegible] *1984).* A cold crystalloid cardioplegic solution was administered [illegible] root and repeated every 15 minutes and when the myocardial temperature drifted above 15° C. Myocardial temperature was not allowed to fall below 8° C. In patients with combined valve and coronary artery operations, the cardioplegic solution was delivered simultaneously through the root and through the free end of each graft after completion of each distal anastomosis. Each liter of cardioplegic solution contained 2.5% dextrose, 0.45% sodium chloride, 5 mEq of sodium bicarbonate, and 20 mEq of potassium chloride; the temperature was 4° C, the pH 7.8 at 25° C, and the osmolarity 305 mOsm. After the first liter, the concentration of potassium in the solution was reduced to 5 mEq/L.

Group II (14 patients operated on between Dec. 10, 1984, and May 3, 1986). Blood for the sanguineous cardioplegic solution was collected from the arterial filter of the cardiopulmonary circuit. The hematocrit value of the blood cardioplegic solution was maintained below 20 vol% by the addition of lactated Ringer's solution. An initial bolus of 500 to 1000 ml was administered into the aortic root. Additional doses of cardioplegic solution were given as in group I. Each liter contained 20 mEq of potassium chloride (which was reduced to 5 mEq after the administration of the first liter) and 4.5 mEq of sodium bicarbonate; the temperature was between 8° and 10° C and the pH 7.6 to 7.8 at 25° C.

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Table II. *Parameters during cardiopulmonary bypass*

	Group I	*Group II*	*Group III*	*p (AOV)*
Duration of CPB (min)	180 ± 14	168 ± 16	186 ± 14	NS
Duration of AC (min)	100 ± 6	103 ± 10	101 ± 6	NS
Mean perfusion pressure (mm Hg)	58 ± 3	54 ± 2	53 ± 2	NS
Mean systemic pH at onset of AC	7.36 ± 0.02	7.33 ± 0.02	7.39 ± 0.02	NS
Mean systemic pH during reflow	7.33 ± 0.02	7.34 ± 0.02	7.39 ± 0.02	<0.02
Volume of cardioplegic solution during AC (ml/hr)	2185 ± 170	3852 ± 320	5167 ± 297	<0.001

Legend: CPB, Cardiopulmonary bypass; AC, aortic clamping; AOV, analysis of variance.

and March 1, 1987). As in group II, blood for the sanguineous cardioplegic solution was collected from the arterial filter. After the initial bolus of 500 to 1000 ml into the aortic root, the blood cardioplegic solution was administered continuously at an initial rate of 100 ml/min. The flow rate was adjusted to ensure, as much as possible, that myocardial temperature remained around 12° C and did not fall below 8° C. The composition of the blood cardioplegic solution was identical to that of the solution used for group II.

Measurement of intramyocardial pH. The system used in the continuous monitoring of intramyocardial pH in these patients has been described in more detail in previous publications from our institution.[20,21] A pointed right-angled glass electrode (10 mm in length, 1 mm in diameter) was inserted into the anteroseptal left ventricular wall and fixed with a 5-0 Prolene epicardial suture. The myocardial temperature, at the same depth within the left ventricular wall, was measured with a thermistor probe connected to a Yellow Springs Instrument Corp. meter (Yellow Springs, Ohio) and inserted about 5 mm away from the pH electrode. The reference electrode was placed in a beaker (at room temperature) containing potassium chloride 3 mEq/L. The circuit was completed with a potassium chloride–agar bridge inserted subcutaneously in the patient's forearm. The system was calibrated in two buffers at two temperatures before and after each case. The outputs from the electrode (in millivolts) and thermistor (in degrees centigrade) were continuously recorded on a two-channel model 1242 recorder (Soltec Corp., Sun Valley, Calif.). At the end of each case, these outputs, along with the electrode calibration, were entered into a computer that generated a plot of the temperature-corrected pH values based on the Nernst equation. For the period of aortic clamping, integrated mean pH and temperature were calculated by planimetry of these plots, as described previously.[21] Measurements made in the anteroseptal region in all patients constituted the data for this study.

Clinical assessment. Left ventricular mass (LVM) was measured retrospectively by a single observer using the right anterior oblique projection of the preoperative ventriculogram according to the formula: LVM = (0.90 × left ventricular volume) + 15, where LVM is expressed in grams.[25] Radionuclide assessment of left ventricular ejection fraction was done preoperatively with technetium 99m pertechnetate. One to 2 weeks postoperatively, repeat radionuclide studies were performed by the same technique. Pharmacologic agents and their dosages used during the course of the operation were recorded [illegible]

electrocardiograms were reviewed by a single observer who was unaware of the type of cardioplegic solution used. Creatinine kinase and its MB fraction were collected at 8-hour intervals in the immediate postoperative period.

Calculations and data analysis. On the basis of our previous assessment of the determinants of intramyocardial acidosis during cardiac operations in man,[26] the patients in the three groups were matched so that no significant differences would be elicited (by analysis of variance) between the groups in regard to the following parameters: left ventricular mass, preoperative left ventricular end-diastolic pressure, myocardial pH at the onset of aortic clamping, duration of cross-clamp period, and duration of cardiopulmonary bypass period. In addition, the groups were also matched according to the mean temperature during the aortic cross-clamp period. Myocardial hydrogen ion concentration data were calculated from the pH data, as previously described,[27] and expressed in nanomoles per liter as $[H^+]$. The acid-base status of the myocardium in the face of fluxes in myocardial temperature was defined by an algorithm developed to calculate the difference at each point in time between myocardial pH and that of the pH of water at that temperature, assuming the pH of water to be 7.45 at 0° C, 7.0 at 25° C, and 6.8° at 37° C.[28,29] Since the pH of water is that of neutrality, this calculated difference between myocardial pH and that of neutrality is referred to in this paper as *delta pHn* and is symbolized by ΔpHn. It is illustrated in an example in Fig. 2.

Data among the three groups were compared by one-way analysis of variance. If the F value was significant, differences between each two of the three groups were analyzed by the Student's *t* test. Where applicable, a χ^2 test was used for comparison of proportions between the groups. A probability value of less than .05 was considered statistically significant. Cumulative data were expressed as mean ± standard error of the mean.

Results

As shown in Table II, there were no significant differences among the three groups in the duration of cardiopulmonary bypass, the mean perfusion pressure during bypass, the mean systemic pH at the onset of aortic clamping, and the duration of the period of aortic clamping. The systemic pH during the period of reflow was slightly higher in group III than in either of the other two groups. There were significant differences in

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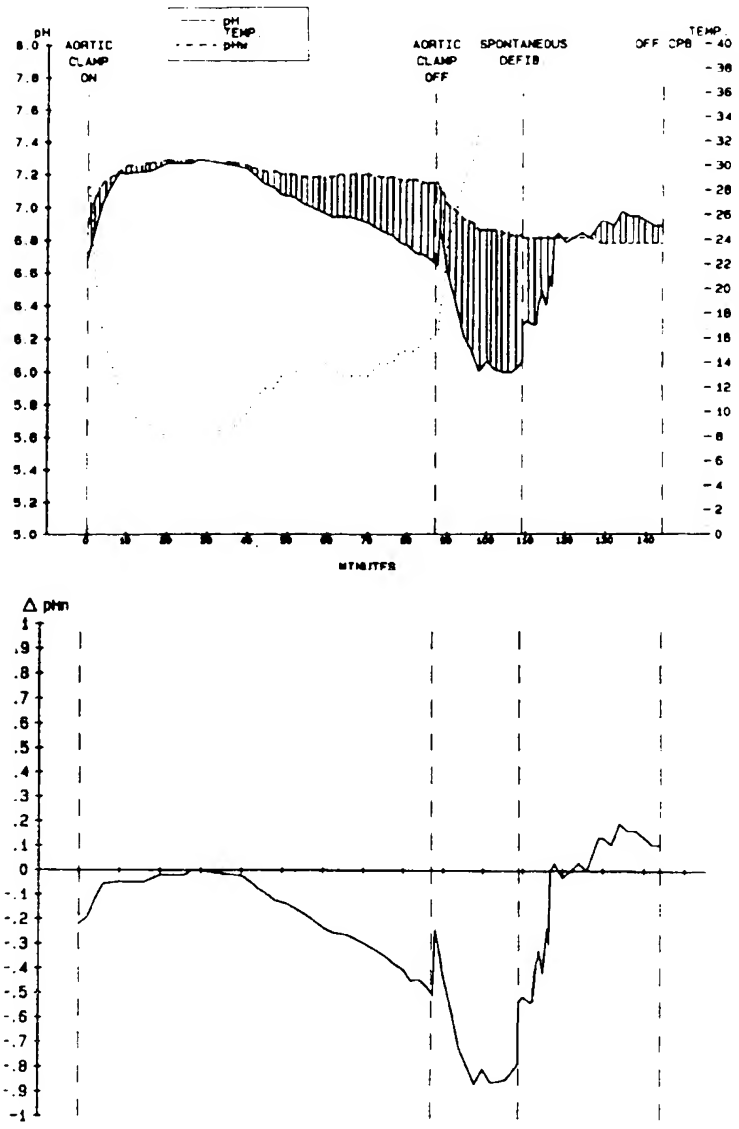

Fig. 2. Shown in the upper panel are myocardial pH, temperature, and the pH of neutrality, ie, of water *(pHw)*, in a patient undergoing aortic valve replacement. The difference between the measured myocardial pH and the calculated pHw, indicated by the *lined area*, quantitates the net changes in the acid-base balance and is referred to as ΔpHn. The *lower panel* illustrates a plot of ΔpHn for the same patient. A positive value of ΔpHn represents relative alkalosis and a negative value of ΔpHn indicates a relative acidosis. Note that significant acidosis occurred during the latter part of the cross-clamp period and during the early phase of reperfusion. A prompt reversal of this acidosis occurred following defibrillation *(DEFIB)*. *CPB*, Cardiopulmonary bypass.

the volume of the cardioplegic solution delivered to each patient group.

Changes in myocardial pH and temperature during the period of aortic clamping. Fig. 2 is a representation of the pH and temperature changes observed in one patient during and after the period of aortic clamping. It also demonstrates the concept of ΔpHn and how it is calculated. Fig. [illegible] shows the cumulative myocardial temperature, pH, $[H^+]$, and ΔpHn data at 5-minute intervals throughout the period of aortic clamping in all three groups. As shown in Fig. 3 and Table III, there was no difference in the mean integrated myocardial temperature among the groups and all three of them achieved the same degree of myocardial cooling throughout the period of aortic clamping. There were also no significant differences in myocardial pH over

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cardial [H⁺], and ΔpHn among the groups at the onset of the period of aortic clamping. Throughout the period of aortic clamping, myocardial pH in group I fell significantly ($p < 0.0001$), which indicates a marked and progressive increase in tissue acidosis, evidenced also by a significant negative increase in ΔpHn ($p < 0.0001$). In contrast, the pH in group III rose throughout the period of aortic clamping; however, this rise was not statistically significant and there was no net change in acid-base balance throughout the period of aortic clamping, as evidenced by ΔpHn, which did not significantly change in this group during this period. In group II, the changes in pH, [H⁺], and ΔpHn throughout the period of aortic clamping were closer to those observed in group III than to the changes observed in group I. They did, however, exhibit progressive tissue acidosis evidenced by a significant negative increase in ΔpHn throughout this period ($p < 0.0001$). When the calculated differences between the values at the beginning and at the end of the period of aortic clamping were compared (Fig. 4), significant differences among all three groups were observed in all three acid-base parameters. These data pointed to an incremental increase in the degree of tissue acidosis during the period of aortic clamping as the method of myocardial protection varied from continuous cold blood, to intermittent cold blood, to intermittent crystalloid cardioplegia.

Changes in myocardial pH and temperature during the period of reperfusion. Wide and nonuniform fluxes in myocardial temperature were observed among the patients during the period of reflow. In view of this, the magnitude of tissue acidosis was best quantitated by the calculation of ΔpHn. Fig. 5 shows these calculated data at 5 points in time after the release of the aortic clamp. At release of the aortic clamp, ΔpHn indicated more severe acidosis in group I (−0.78 pH units) than in the other two groups ($p = 0.0005$). The most acidic ΔpHn during the period of reflow in group I was −0.76 ± 0.05 pH units; it was reached 4.2 ± 1.4 minutes after release of the cross-clamp and was not significantly different from the value at release of the cross-clamp. In group II, the most acidic ΔpHn during reflow was −0.47 ± 0.04; it was observed 3.5 ± 1.05 minutes after cross-clamp release and again was not significantly different from the value at cross-clamp release (−0.44 pH units). In group III the pattern was different; ΔpHn at the time of cross-clamp release was −0.26 pH units, and it increased significantly ($p = 0.028$) to −0.57 ± 0.07 pH units 9.5 ± 2.1 minutes after cross-clamp release. These data indicated that a significant amount of acidosis was observed during reflow in all three groups and that although it was of a less magnitude in the two blood cardioplegia groups than in the crystalloid group, the continuous administration of blood cardioplegia tried to

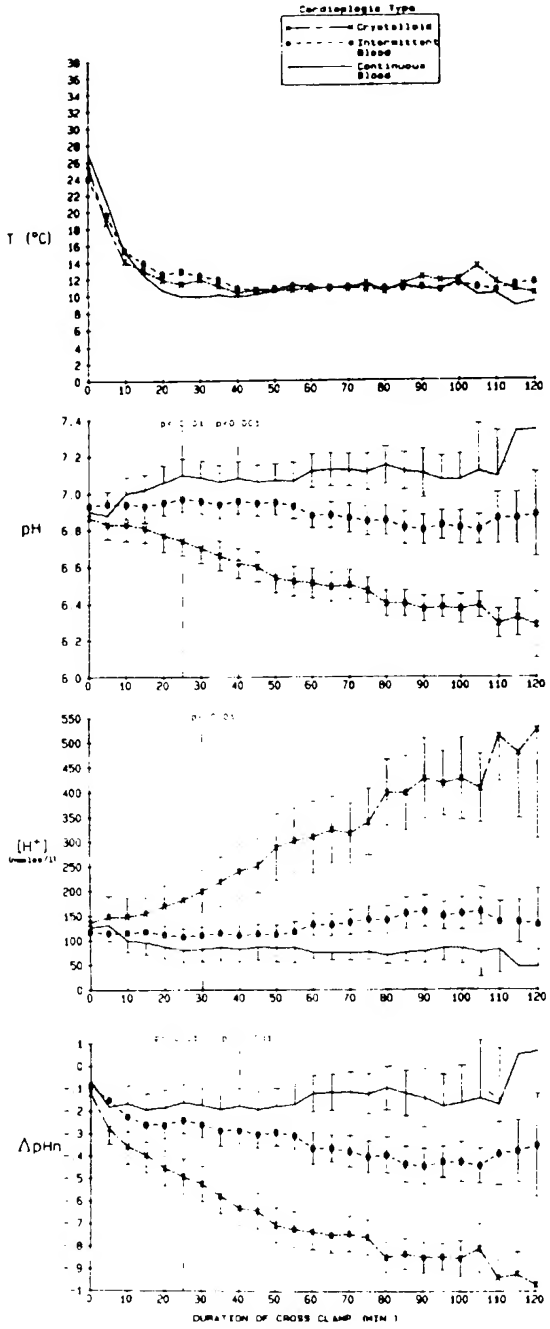

Fig. 3. Cumulative time courses of myocardial temperature *(T)*, pH, [H⁺], and ΔpHn are shown for the three groups during the cross-clamp period. Myocardial temperature was virtually identical among the three groups. Myocardial pH and ΔpHn decreased and [H⁺] steadily increased in the crystalloid group *(broken line)*. In contrast, myocardial pH and pHn increased, and [H⁺] decreased in the continuous blood group *(solid line)*. [illegible] in time when the values for the three groups became statistically different [illegible]

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Table III. *Myocardial pH, [H+], ΔpHn, and temperature data during and after aortic clamping (AC)*

	Group 1	Group 2	Group 3	p (AOV)
At onset of AC				
Myocardial temperature	25.7 ± 0.9	23.9 ± 0.7	28.9 ± 0.8	<0.007
Myocardial pH	6.87 ± 0.07	6.95 ± 0.06	6.78 ± 0.08	NS
Myocardial [H+]	163.4 ± 29.8	149. ± 22.6	193.6 ± 32.8	NS
Myocardial ΔpHn	−0.121 ± 0.070	−0.064 ± 0.057	−0.152 ± 0.069	NS
At 60 min after AC				
Myocardial temperature	10.5 ± 0.9	11.7 ± 0.8	10.8 ± 0.6	NS
Myocardial pH	6.51 ± 0.08	6.87 ± 0.07	7.07 ± 0.10	<0.0003
Myocardial [H+]	390.5 ± 73.8	143.6 ± 21.5	127.5 ± 40.7	<0.002
Myocardial ΔpHn	−0.734 ± 0.084	−0.356 ± 0.061	−0.185 ± 0.098	<0.002
Integrated mean during AC				
Myocardial temperature	12.9 ± 0.4	12.5 ± 0.6	12.3 ± 0.6	NS
Myocardial pH	6.59 ± 0.07	6.91 ± 0.06	7.03 ± 0.08	<0.0002
Myocardial [H+]	295 ± 42.4	136.6 ± 19	127.3 ± 25.3	<0.001
Myocardial ΔpHn	−0.612 ± 0.068	−0.306 ± 0.054	−0.235 ± 0.086	<0.001
At release of AC				
Myocardial temperature	13.9 ± 0.8	11.2 ± 0.8	12.5 ± 0.5	<0.05
Myocardial pH	6.41 ± 0.06	6.79 ± 0.06	6.95 ± 0.10	<0.0001
Myocardial [H+]	430.1 ± 54.9	175.7 ± 26.6	138.6 ± 42.0	<0.002
Myocardial ΔpHn	−0.776 ± 0.061	−0.438 ± 0.059	−0.260 ± 0.099	<0.0002
At discontinuation of CPB				
Myocardial temperature	37.9 ± 0.5	36.9 ± 0.6	38.2 ± 0.2	NS
Myocardial pH	7.11 ± 0.02	7.11 ± 0.05	7.15 ± 0.06	NS
Myocardial [H+]	78.3 ± 0.4	82.8 ± 0.8	75.1 ± 9.9	NS
Myocardial ΔpHn	0.33 ± 0.02	0.31 ± 0.05	0.39 ± 0.06	NS

Legend: AC, Aortic clamping; AOV, analysis of variance; CPB, cardiopulmonary bypass; [H+], hydrogen ion concentration; ΔpHn, difference from pH of neutrality.

prevent reflow acidosis. As shown in Fig. 5, defibrillation elicited a significant rise in ΔpHn in all three groups. At the discontinuation of cardiopulmonary bypass, ΔpHn was positive in all three groups with no differences among them (Table III, Fig. 5).

Clinical relationships. All patients in the study were successfully weaned from cardiopulmonary bypass. Table IV summarizes the results of the outcome in the parameters investigated. The two operative deaths in the study were not related to a low output state; one was due to late massive sepsis and the other was due to generalized bleeding caused by an unexplained severe coagulopathy. The need for inotropic and mechanical support during the weaning and in the immediate postoperative period was significantly greater in group I than in either group II or group III. The requirement for significant support was similar in the latter two groups. Of the nine patients who required significant intraoperative support in group I, eight patients needed an intra-aortic balloon. In contrast, only two of the four patients who required significant support in either group II or group III required an intra-aortic balloon ($p = 0.017$ by χ^2 test comparing sanguineous to asanguineous cardioplegia). There were no differences among the groups in the incidence of postoperative Q wave infarcts by electrocardiogram, and in the levels of postoperative creatine kinase isoenzymes.

Discussion

Ventricular hypertrophy increases the susceptibility of the myocardium to ischemic damage and renders it more difficult to preserve during cardiac operations.[23, 30-33] We[23] have recently demonstrated that, in patients with left ventricular hypertrophy undergoing cardiopulmonary bypass, the administration of a simple cold potassium crystalloid cardioplegic solution failed to provide complete protection against both ultrastructural ischemic damage and the metabolic accumulation of H^+ during and immediately after the period of aortic clamping. The present study compares the efficacy of three modalities of myocardial protection in their ability to prevent such H^+ accumulation in patients with left ventricular hypertrophy undergoing periods of aortic clamping in excess of 75 minutes. It demonstrates that the greatest diminution in H^+ accumulation occurs when a blood potassium cardioplegic solution is continuously infused throughout the period of aortic clamping.

Why not a randomized study? The study design did

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not include randomization of the patients to the three study groups; instead, a matching process based on certain parameters was used. The reason for this is twofold. First, analysis of data obtained from 150 patients in whom continuous measurements of intramyocardial pH were obtained intraoperatively in our institution had indicated that, in addition to myocardial temperature, there were at least six possible factors (listed in the *Results* section) that determined the degree of myocardial acidosis observed during aortic clamping.[26] All these factors had to be kept similar in all three study groups. For a randomization process to yield three groups in which all these factors are comparable would require a much larger number of patients and would make it a less feasible study for us to conduct in a timely manner. The second reason for not using a randomized study design relates to observations made in previous experimental and clinical studies at our institution. Our animal laboratory studies[24, 34] demonstrated that the administration of a blood cardioplegic solution markedly reduced the degree of H^+ accumulation during aortic clamping when compared to a similarly administered crystalloid cardioplegic solution. Our studies[21, 22] in patients undergoing cardiac operations showed that the mean myocardial pH during the period of aortic clamping was a good clinical indicator of the adequacy of myocardial preservation, and that simple cold potassium crystalloid cardioplegia failed to achieve complete protection of the hypertrophied heart undergoing a prolonged period of aortic clamping.[21] These findings were compelling enough to prompt us to use blood cardioplegia and to refrain from randomization in patients with ventricular hypertrophy, combined valvular and coronary artery disease, and anticipated lengthy cross-clamp times.

Assessment of tissue acidosis in the face of changing temperatures. In this study, tissue acidosis was expressed not only by the measurement of tissue pH but also by the quantitation of the $[H^+]$ and by developing an algorithm, illustrated in Fig. 3, relating tissue pH at any one point in time to the pH of neutrality of water. This algorithm was necessitated by the wide variations in myocardial temperature observed in the course of an operation, since the interpretation of changes in myocardial pH and $[H^+]$ is dependent on the physiologic relationship between myocardial pH and temperature. It is now well recognized that hypothermia per se raises the pH of blood and tissues by a factor of 0.015 to 0.022 pH units per degree centigrade.[29, 35, 36] Our studies in patients[20, 21, 37] have repeatedly demonstrated a significant initial rise in myocardial pH with cooling and our laboratory studies have shown

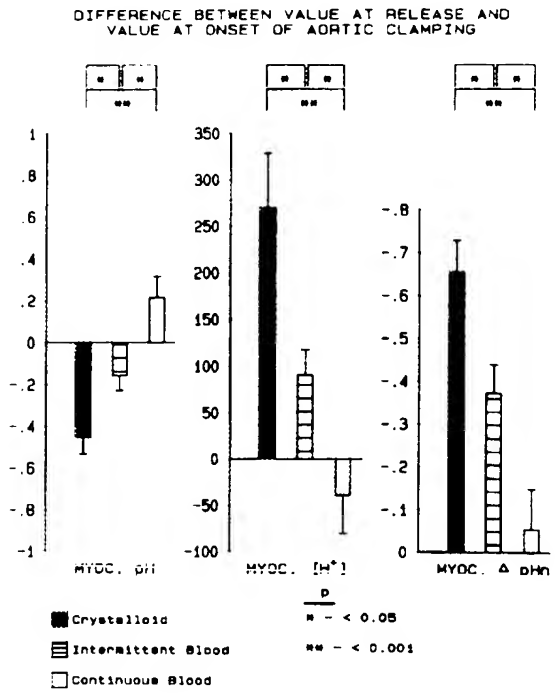

Fig. 4. Changes in myocardial pH, $[H^+]$, and ΔpHn during the cross-clamp period were most severe in the crystalloid group and least pronounced in the continuous blood group. Intermittent blood cardioplegia produced changes that were intermediate in magnitude when compared to the other two groups.

hypothermia per se and not due to either the alkalinity of the bicarbonate-buffered cardioplegic solution or to the effect of washout of acid metabolites.[38] Rahn, Reeves, and Howell[28] have emphasized that the increase in pH with body cooling closely follows the change in neutrality of water. The pH of neutrality of water, or 0.5 pKw, is nearly 7.45 at 0° C and 6.8 at 37° C. Hence a proportionate rise in blood and tissue pH with cooling does not represent a net change in acid-base balance, and failure of pH to rise with cooling would actually indicate relative *acidosis*. Thus the algorithm devised related the myocardial pH at any point in time to that of neutrality, and ΔpHn was calculated assuming that the two paralleled each other in the face of changing temperature.

Salutary effects of continuous sanguineous cardioplegia in the hypertrophied hearts. All three expressions of myocardial pH in our study indicated a marked superiority of blood over crystalloid cardioplegia in the prevention of myocardial tissue acidosis during the [illegible] clamping and reflow. Numerous severe

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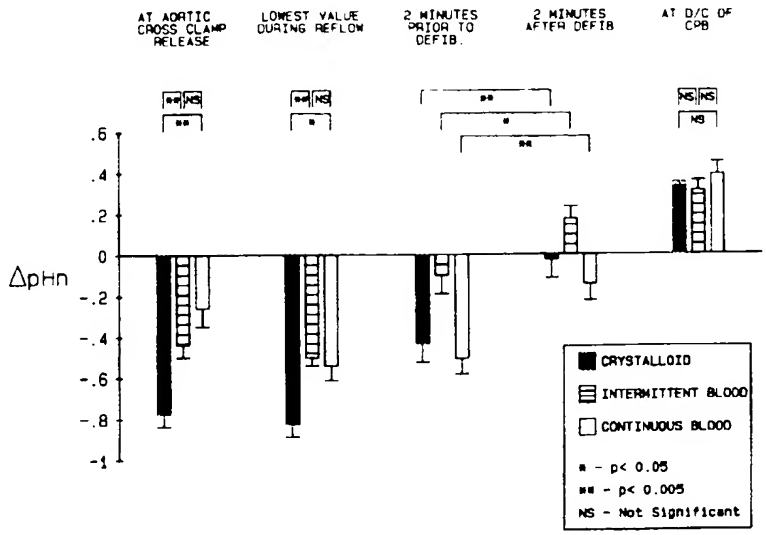

Fig. 5. Shown are the ΔpHn values for the three groups during various phases of reperfusion. Of note is that significant acidosis occurred in all three groups during the early period of reperfusion. Defibrillation produced an immediate reversal of this acidosis in all groups. At the time of discontinuation *(D/C)* of cardiopulmonary bypass *(CPB)*, ΔpHn values were no longer significantly different among the three groups.

Table IV. *Clinical outcome*

	Group 1	*Group 2*	*Group 3*	p
Mortality	1/14	0/14	1/14	NS
Inotropic/IAB support	9/14	4/14	4/14	0.017
Q wave infarct (ECG)	1/14	0/14	1/14	NS
CK isoenzyme (IU/L)				
0 hr postop.	91.6 ± 13.1	113.7 ± 21.8	91.5 ± 16.6	NS
8 hr postop.	97.4 ± 14.4	124.1 ± 20.2	80.3 ± 17.1	NS
16 hr postop.	76.3 ± 8.2	90.4 ± 21.6	86.4 ± 16.4	NS
LV ejection fraction (%)				
Preop.	43.6 ± 2.9	40.9 ± 3.0	48.2 ± 4.0	NS
Postop.	45.5 ± 2.6	41.4 ± 4.5	48.3 ± 3.9	NS
Post.-pre.	+3.3 ± 2.1	+1.5 ± 3.0	+2.2 ± 2.4	NS

Legend IAB, Intra-aortic balloon; ECG, electrocardiogram; CK, creatine kinase; LV, left ventricular; NS, not significant

imental[1-10] and clinical[11-19] studies have been published comparing these two modalities of cardioplegic protection. Unlike most of the other clinical studies, the present study addressed a specific group of high-risk patients and used, for the first time, an on-line assessment of the degree of intraoperative myocardial acidosis throughout the periods of aortic clamping and reflow. A number of factors could have contributed to the salutary effect of blood cardioplegia in the prevention of myocardial acidosis demonstrated in this study. *First*, blood may have delivered more oxygen to the myocardium,[39] but its capacity to deliver oxygen at low temperatures is doubtful. *Second*, blood is an excellent [illegible] buffer because of its varied protein contents and in particular the imidazole ring of histidine. This has been underscored in animal studies that demonstrated a reduction in myocardial acidosis and an improvement in cardiac function by the use of crystalloid solution containing histidine.[41-43] *Third*, the diminished accumulation of H^+ during the cross-clamp period in group 3 may have reflected an increased washout of acid metabolites, since this group received more cardioplegic solution than the other two groups. However, previous work from our laboratory[38] demonstrated a minimized role of decreased washout in acid accumulation, and [illegible] the [illegible] of

cardioplegic solution delivered during ischemic arrest have either compared single-dose to multiple-dose infusion of the solution[3, 44] or have failed to control myocardial temperature.[45] Hence the potential effect of an increase in the washout of acid metabolites during the continuous administration of blood cardioplegia remains uncertain. *Fourth,* the content of calcium in the blood may play an important role in its myocardial protective effect, as suggsted by the recent experimental studies of Heitmiller and associates.[46] Needless to say, the relative contribution of each of these four factors to the overall protective effect of blood cardioplegia cannot be appreciated from the data presented in this study; it awaits clearer definition through a series of specifically designed clinical and experimental studies.

Significance of the pH changes observed during reflow. Of interest in this study are the pH changes observed in the reflow period after the period of aortic clamping. Since myocardial temperature varied between the groups during this period, the degree of acidosis was best assessed by calculating ΔpHn. A significantly negative ΔpHn was observed in all three groups within the first 10 minutes of reflow (Fig. 5). This observation indicates that none of the protective modalities used during the period of aortic clamping was effective in preventing myocardial tissue acidosis during reperfusion. In groups I and II, the acidosis during this period was probably an extension of the acidosis observed at the end of the period of aortic clamping, since ΔpHn during both periods remained unchanged in both groups. In group III, however, a significant negative increase in ΔpHn was observed during reflow when compared to the end of the period of aortic clamping. This observation underscores the failure of continuous cold blood potassium cardioplegia to maintain its protective effect against acidosis beyond the period of aortic clamping. These observations may be interpreted as indicative of a reperfusion injury and should underscore the current efforts at modifying the reperfusion milieu in the course of a cardiac operation.[47, 48] The significant decrease in myocardial acidosis observed after defibrillation in this study (Fig. 5) was similar to the decrease reported in our previous study[37] and underscores the adverse effect of ventricular fibrillation during the reperfusion period.

Clinical implication. The sample size of this study limited its ability to generate data that would elucidate fully the clinical relevance of the changes observed in myocardial tissue acid-base balance in the three groups of patients studied. For example, to elucidate a 5% difference in mortality or in the incidence of postoperative myocardial infarction between the groups at $p < 0.05$ and still maintain statistical power [illegible] minimum number of 274 patients will be required for this study.[49] Nevertheless, one clinical relationship could be elucidated which confirmed in part the myocardial pH data: Patients receiving a crystalloid cardioplegic solution required significantly more inotropic and mechanical support to be weaned from cardiopulmonary bypass than patients receiving blood cardioplegia. In the latter group of patients, however, no added advantage of the continuous over the interrupted mode of administration was demonstrated. Our previous clinical studies[21, 22] demonstrated a direct relationship between myocardial pH during aortic clamping and a clinical myocardial preservation "score." Experimental studies from our laboratory[33, 50] and from other institutions[51-53] in animals undergoing cardiopulmonary bypass have shown that myocardial pH during the period of aortic clamping was a good indicator of the adequacy of preservation of myocardial function and ultrastructure. Thus it is reasonable to postulate that, of the three groups of selected high-risk patients studied, those receiving continuous cold blood cardioplegia are likely to attain the best myocardial protection during prolonged periods of aortic clamping.

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Discussion

Dr. Tomas A. Salerno *(Toronto, Ontario, Canada)*. A countryman and a Brazilian by the name of Dr. Bomfim,[1] while studying in Stockholm, reported a similar series of aortic valve replacements in patients using continuous oxygenated blood cardioplegia. [illegible] sophisticated methods to describe the metabolic changes, his results were similar [illegible]

My colleague, Dr. Lichtenstein, and I have been very interested in continuous oxygenated blood cardioplegia and have used the technique in over 800 patients with results comparable to those reported by Dr. Khuri in terms of myocardial function and metabolism. The distressing thing is that in the laboratory, using a hypertrophied pig model, we were unable to show any differences between hypertrophied hearts using intermittent versus continuous cardioplegia. Perhaps this underscored the fact that we are unable to assess function and metabolism using as sensitive methods as Dr. Khuri did.

I have some very simple questions for Dr. Khuri: Does he think there is the need to administer blood cardioplegia at such a low temperature, as the oxygen dissociation curve may offset the delivery of oxygen? Second, has he considered using this technique for other types of cardiac operations? We have used it in all of our cardiac procedures. Third, can he tell us something about neonatal hearts, which we believe may benefit from this technique. Finally, does he foresee pH measurement as a new method of assessing the adequacy of protection?

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Dr. Mark V. Braimbridge *(London, England)*. I come from a lesser developed nation in the United Kingdom and my hospital has to be convinced that blood cardioplegia is that much better than crystalloid cardioplegia if it is going to be able to afford the elegant equipment that is required.

The problem about most of the papers comparing blood cardioplegia with crystalloid cardioplegia is that they compare it with second-class crystalloid solutions. To emphasize this point, Lary Robinson, now in Omaha, compared all crystalloid solutions that were being used at Duke at that time. They were dextrose saline with potassium, which is the solution used by Dr. Khuri's group, lactated Ringer's with potassium, Tyer's solution, and the St. Thomas' Hospital solution. With creatine kinase release used as an index of the left ventricular damage, the St. Thomas' Hospital solution was statistically significantly better than the others, and particularly better than the one used by Dr. Khuri.

We also compared the original solution that we used for the first 10 years from 1975 at St. Thomas' Hospital with the newer solution now made by Abbott Laboratories, North Chicago, Illinois, and called Plegisol. If these are compared in an isolated rat heart with 3 hours of cardioplegic arrest at 20° C, even these two solutions can be shown to be significantly different: There was 70% recovery with Plegisol solution, compared with only 15% with the original solution.

We also investigated adding oxygen to the crystalloid solutions. Assessing our original solution after 3 hours of hypothermic aortic occlusion in the isolated rat heart, we found that the unoxygenated solution allowed a 20% recovery [illegible] of the solution was oxygenated this recovery significantly improved [illegible] However [illegible] without oxygen was much better than the oxygenated origina[illegible]

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solution. To show any advantage from adding oxygen to Plegisol solution, we had to increase the hypothermic arrest to 4 hours, which was a very long time for a rat heart, and then we could show a difference.

I would like to make a plea that when expensive equipment for blood cardioplegia is recommended for use in Europe, the experimental study should use an effective cardioplegic solution and should also evaluate the results of oxygenating the crystalloid solution. This is very cheap and merely requires putting a needle into the bag and bubbling oxygen into it.

Dr. Khuri *(Closing).* I would like to thank the discussants for their thoughts and contributions. In response to Dr. Salerno's questions, we are currently investigating the optimal level of myocardial hypothermia; our initial data suggest that there is added protection by bringing the myocardial temperature to levels below 15° C. Whether myocardial temperature levels below 12° and 10° C afford additional metabolic protection is currently under investigation in both our animal laboratory and our operating room. We do not use continuous cold blood cardioplegia in *all* our patients; we use it routinely in patients with valvular heart disease or patients with left ventricular hypertrophy in whom we anticipate a cross-clamp time of more than 1 hour. Since the differences in pH among the three types of protection used in this study did not become appreciable before 45 minutes of aortic clamping, and since by far most of our cross-clamp periods for coronary revascularization do not exceed 1 hour, we see no advantage in using blood over crystalloid cardioplegia in the routine coronary case. We find that the use of crystalloid cardioplegia in this setting cuts down the time required to perform the distal anastomoses because it facilitates the exposure more than blood cardioplegia. We have no data regarding myocardial pH in the neonatal heart simply because we only operate on the veteran population. In the adult patient, our data clearly show an advantage to the use of pH measurement as a routine monitor of the adequacy of myocardial preservation. We are currently developing the methodology that will make it easy and practical to perform in the operating room.

I appreciate Dr. Braimbridge's comments, and I agree with him that the crystalloid cardioplegic solution that we used in this study may have been "second-class." Our studies have clearly shown that sodium bicarbonate in the dosages commonly used is a poor buffer and elicits very little effect on myocardial pH. The use, in the crystalloid cardioplegic solution, of a more potent buffer such as histidine, for example, may have resulted in less myocardial acidosis. The purpose of our study, however, was not to determine the most optimal crystalloid cardioplegic solution, but to compare a frequently used crystalloid solution to blood cardioplegia. The crystalloid solution we used was commonly used at the time of the study and many centers continue to use it today. Our study does not claim that *all* crystalloid solutions are inferior to blood as cardioplegic vehicles.